STUDY ON APPROPRIATENESS AND COST COMPARISON OF PRESCRIPTION OF PROTON PUMP INHIBITORS AT A TERTIARY CARE HOSPITAL

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CERTIFICATE

This is to certify that the M.Pharm Dissertation entitled **"Study on Appropriateness and Cost Comparison of Prescription of Proton Pump Inhibitors at a Tertiary Care Hospital"** being submitted to The Tamil Nadu Dr. M.G.R Medical University, Chennai was carried out by **Ms. Pheba Susan Thomas** in the Department of Pharmacy Practice, College of Pharmacy, Sri Ramakrishna Institute of Paramedical Sciences, Coimbatore, under the direct supervision and guidance of **Mr. V. Shivashankar, M.Pharm, (Ph.D).,** Assistant Professor, Department of Pharmacy Practice, College of Pharmacy, Sri Ramakrishna Institute of Paramedical Sciences, Coimbatore.

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CONTENTS

LIST OF ABBREVIATIONS

AGE	:	Acute Gastroenteritis
APD	:	Acid Peptic Disease
ASDs	:	Anti-secretory Drugs
AST	:	Acid Suppressive Therapy
B.D	:	Twice daily
CDAD	:	Clostridium difficile associated Diarrhoea
COPD	:	Chronic Obstructive Pulmonary Disease
CVA	:	Cerebrovascular Accident
DDDs	:	Defined Daily Doses
DM	:	Diabetes Mellitus
DU(s)	:	Duodenal Ulcer(s)
EE	:	Erosive Esophagitis
FDA	:	Food and Drug Administration
GERD	:	Gastroesophageal Reflux Disorder
GI	:	Gastrointestinal
GP(s)	:	General Practitioner(s)
GU	:	Gastric Ulcer
H. pylori	:	Helicobacter Pylori
$H_2RA(s)$	:	Histamine-2 Receptor Antagonist(s)
ICU	:	Intensive Care Unit

IV	:	Intravenous
NSAID (s)	:	Non-steroidal anti-inflammatory drug(s)
O.D	:	Once daily
OTC	:	Over-the-counter
PPI(s)	:	Proton Pump Inhibitor(s)
PUD	:	Peptic Ulcer Disease
SHT	:	Systemic Hypertension
SUP	:	Stress Ulcer Prophylaxis
T.I.D	:	Three times a day
TB	:	Tuberculosis
UTI	:	Urinary Tract Infection
WHO	:	World Health Organization
ZES	:	Zollinger-Ellison syndrome

ABSTRACT

Proton-pump inhibitors (PPIs) remain the leading evidence-based therapy for upper gastrointestinal disorders, including GERD, dyspepsia, and PUD. The effectiveness of PPIs has led to overutilization in multiple treatment areas, exposing patients to an increasing number of potential risks. The overutilization of PPIs in ambulatory care settings is often a result of failure to re-evaluate the need for continuation of therapy. Despite clear indications for long-term PPI therapy, many patients continue to over-utilise these medications inappropriately without re-evaluation. A potential consequence of prolonged PPI therapy is the potential for long term hyper-gastrinemia and parietal cell hypertrophy.

PPIs are frequently used in patients who do not meet the criteria for appropriate use and where less powerful, cheaper agents would be effective for the treatment of symptoms. Even though the indications for PPI prescription are well defined by U.S FDA, these indications are often ignored. Reducing inappropriate prescribing of PPIs in the inpatient and outpatient settings can minimize potential for adverse events, and can also help in controlling cost expenditure.

The objective of the study is to determine the appropriateness and compare the cost of prescriptions of PPIs in the selected study population as per the inclusion criteria. The prospective observational study was conducted. The data was collected during regular ward rounds and was analysed. The appropriateness was analysed using the FDA guidelines.

A total of 209 patients were included in the study, their prescriptions were analysed to determine appropriateness. The study population was categorised under different risk groups based on the number of risks. The different risks in the

study population was found to be age, stress related profession, use of alcohol, smoking and chronic NSAID users. The patients were categorised into 4 main groups, i.e. no risk, moderate risk, high risk and very high risk categories. Majority of the patients 83 (39.71%) came under the moderate risk category, followed by 64 patients (30.62%) in the low risk category, 52 patients (24.88%) in the high risk category and 10 patients (4.79%) in the very high risk categories.

The total number of drugs prescribed for the study population was found to be 2024. A total of 285 (14.08%) antibiotics were prescribed, followed by 209 (10.33%) PPIs, 155 (7.65%) anti-diabetics, 132 (6.32%) anti-hypertensives, 129 (6.18%) NSAIDs, 115 (5.51%) anti-emetics and others. Among the 209 PPIs prescribed in the study population pantoprazole was the most frequently prescribed 144 (68.89%). Esomeprazole 46 (22.01%) comes next in line followed by rabeprazole 17 (8.13%) and omeprazole 2 (0.95%).

Appropriateness of prescription of PPIs in the study population was analysed using the FDA guidelines, out of 209 patients 115 (55.02%) were found to be appropriately prescribed with PPIs, which indicates there is recommended conditions as mentioned in guidelines and 94 (44.98%) prescriptions were found to be inappropriate, i.e., there was no necessary indication of PPI use as per the guidelines. The inappropriate prescriptions with PPIs were analysed and it was found that inappropriateness in prescriptions may be due to several reasons, i.e. wrong frequency, wrong dosage form, availability of alternative, prolonged duration of treatment, inappropriate indication and occurrence of adverse events. Majority of the inappropriate prescriptions involved pantoprazole followed by esomeprazole and rabeprazole.

The cost of treatment can be reduced in 94 patients who have been prescribed with PPIs inappropriately. Among these 94 patients, 71 patients were identified with H2RAs as an alternate drug instead of PPI by which the cost of treatment will be reduced. An unnecessary healthcare cost to the patient is a matter of concern and necessary action must be taken.

The results reveal that interventions made by the pharmacist avoided the inappropriate use of PPI at the study site. Most of the inappropriate prescriptions were consisting increased frequency of dosing and utilising PPIs for prophylactic use. Reducing PPI use will prevent the risk associated with PPIs and also reduce cost involved with its use. The need for PPI use in the individual patient must be evaluated by the pharmacist and if any possible alternatives are found to be effective the same can be reported to the physician. The regular monitoring of prescription of PPI by clinical pharmacist is the need of the hour.

INTRODUCTION

PUD is common among adults in modern society. It occurs due to imbalance between the aggressive and defensive factors[1]. Approximately 500,000 new cases are reported each year. A variety of psychosomatic, humoral and vascular derangements have been implicated and the importance of Helicobacter pylori (H. pylori) infection as a contributor to ulcer formation and recurrence has been recognized[2].

The physical morbidity associated with this disease justifies the continued interest in its epidemiology. Although the prevalence of PUD is decreasing in many communities, it still affects approximately 10% of adults at some point in their lives. The prevalence is seen to increase with age[3]. The male to female ratio for duodenal ulcer varies from 5:1 to 2:1, whereas that for gastric ulcer is 2:1 or less[4]. The incidence of PUD has fluctuated considerably in the past. The incidence varies with ulcer type, age, gender, and geographic location. The prevalence of PUD has shifted from predominance in men to nearly comparable prevalence in men and women. According to the latest World Health Organisation (WHO) published data in May 2014, PUD deaths in India reached 85,487 or 0.96% of total deaths[5].

Patients with PUD may present with a range of symptoms, from mild abdominal discomfort to perforation and bleeding. The risk factors for peptic ulcers include[4]:

- ✓ H. pylori infection
- ✓ Age greater than 65 years
- ✓ Stress
- ✓ High dose of non-steroidal anti-inflammatory drugs (NSAIDs) or more than one NSAID (including aspirin)

- ✓ Short-term history of NSAID use (<1 month)
- ✓ Hypersecretory condition
- ✓ Smoking
- ✓ Drinking alcohol

Although mortality rates from PUD are low, the high prevalence and the resulting pain, suffering and expense are very costly. The drugs which are commonly used for ulcer therapy are H_2 receptor blockers, proton pump inhibitors (PPIs), ulcer protective agents, antacids and anti-H.pylori drugs[5].

1. Reduction of gastric acid secretion

(a) H_2 receptor antagonists (H_2RAs) : Ranitidine, Famotidine

(b) PPIs : Omeprazole, Lansoprazole, Pantoprazole, Rabeprazole, Esomeprazole

(c) Anticholinergics : Pirenzepine, Propantheline

(d) Prostaglandin analogue : Misoprostol

2. Neutralization of gastric acid (Antacids)

(a) Systemic : Sodium bicarbonate, Sodium citrate

(b) Non-systemic : Magnesium hydroxide, Magnesium trisilicate, Aluminium hydroxide gel, Magaldrate, Calcium carbonate

3. Ulcer protectives : Sucralfate, Colloidal bismuth subcitrate

4. Anti-H. pylori drugs : Amoxicllin, Clarithromycin, Metronidazole, Tinidazole, Tetracycline[4]

Anti-ulcer drugs are mainly used for the treatment of PUD, gastroesophageal reflux disorder (GERD), gastritis and Zollinger-Ellison syndrome (ZES). The main goals of anti-ulcer therapy include relief from pain, promotion of ulcer healing, prevention of complications and prevention of relapse. Various strategies to maintain the disease in remission are continuous or on demand –

intermittent H_2RAs or PPI, maintenance sucralfate or antacid treatment. Out of this continuous maintenance H_2RAs or PPI therapy is regarded as the most effective and convenient[6].

The best approach, however, is to identify and treat H. pylori positive cases. Long term acid suppressive therapy would then be needed only in H. pylori negative cases[4].

PROTON PUMP INHIBITORS (PPIs)

PPIs signify a revolutionary development in gastroenterology. These drugs irreversibly inhibit the gastric H+, K+ ATPase pump and decrease both basal and stimulated gastric acid production. PPIs are successful and cost-effective for the treatment of severe gastro esophageal reflux disorder (GERD) and other acid-related disorders. Prescriptions for PPIs have increased extremely over the last decade[6,7].

PPIs have emerged as the chief treatment for GERD and peptic ulcer disease due to their effectiveness and low toxicity in treating these conditions[6,8]. PPIs are first choice in the treatment of GERD and peptic ulcers for a period of 4-8 weeks. In combination with antibiotics, they are used for abolition of H. pylori infection. After abolition for symptomatic H. pylori infection, continuation of PPI is usually not necessary except when there is another indication. PPIs are also indicated as a simultaneous medication to prevent NSAID and aspirin related ulcers in high-risk patients[9,10].

The available PPIs (such as, pantoprazole, rabeprazole etc.) are equal in effectiveness and safety but differ in cost. PPIs certainly offer an improvement in the treatment of common and important gastrointestinal diseases. They are effective in the cure or prevention of peptic acid disorders and in the management of GERD, esophagitis, gastric ulcer, bleeding peptic ulcer, eradication of H. pylori, dyspepsia, ZES and prevention of gastrointestinal (GI) toxicity induced by NSAIDs[11,12].

PROBLEMS DUE TO PPI OVERUSE

Proton-pump inhibitors (PPIs) remain the leading evidence-based therapy for upper gastrointestinal disorders, including GERD, dyspepsia, and PUD. The effectiveness of PPIs has led to overutilization in multiple treatment areas, exposing patients to an increasing number of potential risks. The overutilization of PPIs in ambulatory care settings is often a result of failure to re-evaluate the need for continuation of therapy. PPI overutilization in the inpatient setting is often a result of inappropriate stress ulcer prophylaxis (SUP) in non-intensive care unit patients, and failure to discontinue SUP prior to hospital discharge[13].

Despite clear indications for long-term PPI therapy, many patients continue to over-utilise these medications inappropriately without re-evaluation. A potential consequence of prolonged PPI therapy is the potential for long term hyper-gastrinemia and parietal cell hypertrophy[11].

The potential risks associated with long-term use include vitamin B12 deficiency, spontaneous bacterial peritonitis in cirrhotic patients with ascites, increased community-acquired pneumonia, diarrhoea due to Clostridium difficile and gastroenteritis due to Campylobacter jejuni. Iron deficiency anemia has been reported in patients with atrophic gastritis or gastric resection. There currently is no data demonstrating the development of iron deficiency anemia in normal subjects on PPI therapy[7].

PPIs also cause headaches and diarrhoea in more than 10% of cases. Studies have revealed that, people who use PPIs are up to 21% more probable to experience a heart attack[9,11].

Risk of Fractures

The Food and Drug Administration (FDA) requires that labeling for PPIs include safety information about a possible increased risk of fractures of the hip, wrist, and spine. This requirement is based on an FDA review of several epidemiological studies with findings indicating that patients who may bear the highest risk for these fractures received a high dose of a PPI or had PPI therapy lasting longer than one year. The majority of these studies included individuals 50 years old or older[5].

Risk of Hypomagnesemia

In March 2011, the FDA published a Drug Safety Communication to inform consumers and health care professionals that long-term use of PPIs can cause hypomagnesemia. In 25% of patients, magnesium supplementation was not sufficient to correct PPI-induced hypomagnesemia; rather, PPI therapy had to be discontinued. The FDA recommends obtaining a serum magnesium level prior to initiation of therapy if a patient is to be on prolonged treatment[5].

Risk of Clostridium difficile-Associated Diarrhea (CDAD)

On February 8, 2012, the FDA published a Drug Safety Communication to inform patients and health care professionals that PPIs may be associated with an increased risk of CDAD. Symptoms of CDAD include abdominal pain, fever, and watery stools. Patients who take a PPI and develop diarrhoea that does not improve should be evaluated for CDAD. Patients with advanced age, certain chronic medical conditions, and patients taking broad spectrum antibiotics are at greatest risk for developing CDAD. The FDA recommends using the lowest dose and shortest duration of PPI[5].

PPIs are frequently used in patients who do not meet the criteria for appropriate use and where less powerful, cheaper agents would be effective for the treatment of symptoms. Although there is evidence about superiority of the PPI over H_2 receptor blockers and others drugs for the treatment of GERD or peptic ulcer, due to their stronger and longer action, other drugs could often be an effective and safe alternative for many patients[10,11]. Even though the indications for PPI prescription are well defined by U.S Food and Drug Administration (FDA), these indications are often ignored[5].

FDA Approved Indications for Proton Pump Inhibitors in Adults[5]

The FDA-approved indications for use include:

1. Healing of erosive esophagitis (EE)
2. Maintenance of healed EE
3. Treatment of GERD
4. Risk reduction for gastric ulcer (GU) associated with NSAIDs
5. H. pylori eradication to reduce the risk of duodenal ulcer (DU) recurrence, in combination with antibiotics
6. Pathological hypersecretory conditions, including ZES
7. Short-term treatment and maintenance of DUs

The FDA approved indications and recommended dosing for each indication is given in **Table 1**.

ROLE OF PHARMACIST IN APPROPRIATE DRUG USE

Table 1: Proton Pump Inhibitors: U.S FDA-Approved Indications and Dosages for Use in Adults[5]

Indication	Treatment
DU	Short-term:- Lansoprazole - 15 mg O.D for 4 weeks Omeprazole - 20 mg O.D Rabeprazole - 20 mg O.D for 4 weeks Maintenance:- Lansoprazole - 15 mg O.D
H.pylori eradication	Esomeprazole - 40 mg O.D, amoxicillin 1000 mg and clarithromycin 500 mg B.D for 10 days Lansoprazole - 30 mg, amoxicillin 1000 mg and clarithromycin 500 mg B.D for 10 or 14 days Omeprazole - 20 mg, amoxicillin 1000 mg and clarithromycin 500 mg B.D for 10 days Rabeprazole - 20 mg, amoxicillin 1000 mg and clarithromycin 500 mg B.D for 7 days
EE	Healing:- Esomeprazole - 20 mg or 40 mg O.D for 4 to 8 weeks Lansoprazole - 30 mg O.D for 8 weeks Omeprazole - 20 mg O.D for 4 to 8 weeks Pantoprazole - 40 mg O.D for 8 weeks Maintenance:- Esomeprazole - 20 mg O.D Lansoprazole - 15 mg O.D Omeprazole - 20 mg O.D Pantoprazole - 40 mg O.D

Indication	Treatment
GERD	Healing:- Rabeprazole - 20 mg O.D for 4 to 8 weeks Maintenance:- Rabeprazole - 20 mg O.D Symptomatic:- Esomeprazole - 20 mg O.D for 4 weeks Lansoprazole - 15 mg O.D for 8 weeks Omeprazole - 20 mg O.D for 4 weeks Rabeprazole - 20 mg O.D for 4 weeks
GU	Short-term:- Lansoprazole - 30 mg O.D for 8 weeks Omeprazole - 40 mg O.D for 4 to 8 weeks Healing (NSAID associated):- Lansoprazole - 30 mg O.D for 8 weeks Risk reduction (NSAID associated):- Esomeprazole - 20 mg or 40 mg O.D for 6 months Lansoprazole - 15 mg O.D for 12 weeks
Heartburn	OTC Treatment:- Lansoprazole - 15 mg O.D for 14 days Omeprazole - 20 mg O.D for 14 days
Hypersecretory Conditions	Esomeprazole - 40 mg B.D Lansoprazole - 60 mg O.D Omeprazole - 60 mg O.D Pantoprazole - 40 mg B.D Rabeprazole - 60 mg O.D

"Appropriateness" has been described as "the next frontier" in the development of health care**.** Appropriateness is a complex issue with different dimensions and definitions and these differ between countries. However, most definitions of appropriateness address a number of key requirements such as; care is effective, efficient and consistent with the ethical principles and preferences of the relevant individual, community or society. The priorities given to each of these dimensions vary in different populations. Ethical values play a central role in determining the priorities given to components of appropriateness[14].

The goal of health services in general is to provide effective care to patients who benefit from it in a manner that is acceptable to the patient and the health care provider, at a cost that is acceptable. A number of strategies are now available to improve appropriateness. The development and use of clinical practice guidelines have been demonstrated to improve the appropriateness of care. Guidelines can be used to shape decisions about access, costs of care and coverage of services. Numerous government agencies and health-related organizations now develop evidence-based clinical practice guidelines[14].

The role of pharmacists has been proven to improve many outcomes regarding patient health, including patient safety, disease and drug therapy management, healthcare costs, medication adherence and quality of life[15]. Pharmacists play a unique role in improving the appropriate use of PPIs within the hospital setting. Responsibilities of the pharmacist are the following[16,17]:

- Restrict administration of PPIs to patients with appropriate indications as per guidelines within both the critical care and general medicine setting and thus help in preventing overutilization of PPIs.

- Inform prescribers about PPI strength abnormalities and practice guidelines available to select most appropriate therapy for individual patient.
- Encourage prescribers to make cost effective choice of PPIs that are clinically appropriate.
- Notify prescribers of PPI safety alerts and clinical updates.
- Enhance quality of patient care and determine opportunities for improvement in care provided.
- Identify adherence and non-adherence with guidelines in prescribing.
- Identify prescription pattern.
- Identify potential prescription related problems such as drug-drug interactions, under or overdosing and inappropriate therapy[17].

The initiation and the continuous use of PPIs without correct indications will result in severe health conditions and subsequently significant costs. Administration of needless medication can also cause adverse effects and pharmacological interactions. Reducing inappropriate prescribing of PPIs in the inpatient and outpatient settings can minimize potential for adverse events, and can also help in controlling cost expenditure.

LITERATURE REVIEW

Anton P et al 2016[18] did a nationwide drug utilization study on the use of proton pump inhibitors among adults. The prevalence of PPI use increased fourfold during the study period. The study concluded that the use of PPIs is extensive and increasing rapidly, especially among the elderly.

Krishna K J et al 2016[19] carried out a prospective observational study on prescribing pattern of acid suppressant drugs in current clinical practice. This study found overuse and underuse of acid suppressant drugs in the study site. The study highlighted the need for a local protocol for rational use of these agents in current clinical practice.

Blesson M et al 2015[20] conducted a study on assessment of appropriateness in the usage of proton pump inhibitors in a tertiary care teaching hospital. The study concluded inappropriate prescription of PPIs without valid indications is prevalent among physicians in the healthcare system. Prescribers must be well conscious regarding usage of PPIs and selection of PPI must be done wisely and should be prescribed to the patients only if indicated.

Minh T H et al 2015[21] studied about acid suppressive therapy for stress ulcer prophylaxis in non-critically ill patients. This literature discourages the use of acid suppressive therapy (AST) for stress ulcer prophylaxis (SUP) in non-critically ill patients. This study came to the conclusion that a large percentage of non-critically ill patients were given AST during their hospital stay; 88.5% of these medications were given inappropriately to patients who were at extremely low risk of gastrointestinal bleeding.

Nirajan K et al 2015[22] conducted a study on proton pump inhibitors in general medicine unit of a tertiary care teaching hospital. Appropriate use of PPIs was found to be 76.93% whereas the inappropriate use was found to be 23.07%. The study recommended use of PPI only when there is documented evidence of a GI disorder that cannot be treated with an H2-receptor antagonist and where a PPI use is clinically justified.

Nousheen et al 2014[23] studied on the rationality of use of proton pump inhibitors in general practice. The incidence of improper use of PPIs varies from 40-70%. The study suggested that awareness should be created among the clinicians in the hospital so that appropriate prescription of PPIs will improve.

Shobha C et al 2014[24] performed a prospective assessment of prescribing pattern of intravenous proton pump inhibitors in an Indian hospital. This study revealed significant inappropriateness of PPI administration with particular reference to indication to use, duration of therapy, and changeover of therapy in an Indian tertiary-care teaching hospital.

Biswa M P et al 2014[25] studied on attitude and knowledge of Indian emergency care residents towards use of proton pump inhibitors. In conclusion the study stated that emergency care residents in India tend to overuse PPIs in a manner similar to their counterparts in developed countries. Specific measures may be helpful in preventing such practices.

Syed H A N et al 2014[26] performed a study on increasing use of proton pump inhibitors in Karachi. The results suggested that PPIs are over prescribed in primary and secondary care setting. There is scope towards more careful and cost-effective PPI prescribing which can improve adherence to evidence based practice and reduce the long term adverse effects of PPIs.

Jessica F et al 2013[27] conducted a study on the potential influence of various initiatives to improve rational prescribing for PPIs. A retrospective observational study was conducted for assessing the influence of multiple initiatives on utilization and expenditure of the PPIs was carried out. Utilization was measured in terms of defined daily doses (DDDs) and DDDs/thousand inhabitants per day. The study stated that multiple reforms influenced utilization patterns and expenditure for the PPIs.

Heidelbaugh J J et al 2012[28] performed a review on proton pump inhibitors overutilization and the risks involved in overusage. This study concluded that prescription of PPI therapy in practice can be guided by several general principles to minimise potential risks. The study recommends that in patients with appropriate indications for PPI therapy, the lowest effective dose should always be prescribed.

Wesam F et al 2012[29] performed a prospective study on prescription patterns of PPIs for prophylaxis of stress-related mucosal disease in patients admitted to the intensive care unit. This study concluded that stress ulcer prophylaxis administration was inconsistent and includes both underutilization and overutilization. Educating physicians and implementing hospital protocols is important to improve PPI prescribing patterns.

Pasina L et al 2011[30] evaluated the prevalence and appropriateness of drug prescriptions for peptic ulcer and gastro-esophageal reflux disease in hospitalized elderly. The study concluded that prevalence of inappropriate prescription of drugs for peptic ulcer or GERD remained almost the same at admission and discharge. Inappropriate use of these drugs is related to the concomitant use of other drugs. Careful assessment of clinical conditions and stricter adherence to evidence-based guidelines are essential for a rational and cost-effective use of drugs for peptic ulcer or GERD.

Soumana C N et al 2010[31] conducted a study on clinical and cost impact of intravenous proton pump inhibitor use in non-ICU patients. Updated guidelines were used to assess the appropriateness of the indication and route of administration. This study highlights the over-utilization of IV PPIs in non-intensive care unit patients. Restriction of IV PPI use for justified indications and route of administration is recommended.

Elena R et al 2010[32] performed a study on overuse of PPIs in patients at admission, during hospitalisation, and at discharge in a tertiary Spanish hospital. The results of this study indicated that there was a very high frequency of overuse of PPIs in inpatients and outpatients.

Craig D G N et al 2010[33] carried out a prospective study on inappropriate utilization of intravenous proton pump inhibitors in hospital practice. This study suggested that the majority of IV PPI prescriptions in hospital were inappropriate. Improving prescribing awareness through education of junior medical staff could reduce inappropriate IV PPI use.

Jacob G H et al 2009[34] retrospectively evaluated the use of intravenous proton pump inhibitors in a teaching hospital. Indications for use were compared with current established guidelines to determine appropriate usage. The conclusion of the study stated that intravenous PPI prescribing habits in the study site were poor.

Nadia B et al 2009[35] carried out a study on the prescribing of PPIs and histamine-2 receptor antagonists (H2RAs) for defined gastrointestinal disorders. The study concluded that prescribing of H2RAs decreased, whereas the prescribing of PPIs increased.

Ahmed Y M 2007[36] performed an observational study on improper use of ASDs in a tertiary care teaching hospital. The main objective was to evaluate the improper use of pantoprazole and ranitidine, and to identify the associated factors for misuse of these two drugs. Improper use of the drugs decreased as duration of hospital stay lengthened. Improper use of ASDs was observed in 43% of the patients. Based on the results of this study, correct measures need to be implemented in order reduce the misuse of ASDs.

Susan J S et al 2005[37] studied on collaboratively designed practice guidelines to promote appropriate use of intravenous PPIs. Patients initiated on IV pantoprazole therapy were evaluated prospectively for appropriateness of therapy. Pharmacists assessed clinical use, dosing strategy, administration route, and prescribing patterns. Evaluation of institutional pantoprazole utilization revealed usage extending beyond indications with proven efficacy. Pharmacists and physicians together developed evidence-based practice guidelines; adherence to these guidelines showed a 50% improvement.

Saad A Z M et al 2005[38] conducted a survey on proton pump inhibitors prescribing in an Irish general hospital. The results suggested that PPIs were over prescribed in hospital practice, and there is scope to improve the quality and cost-effectiveness of PPI prescribing.

Jones M I et al 2001[39] did a study on PPI prescribing by general practitioner (GP). The objective was to compare GPs' usage of different PPIs and evaluate how GPs' prescribing changes following introduction of a cheaper competitor. It was reported that use of new PPIs increased from 6 to 24%. The wide variation in PPI prescribing suggests that there is scope for improvement in the quality and cost of PPI prescribing.

SCOPE OF THE STUDY

PPI overuse is widespread in both primary and secondary care. Concerns have been raised about the increasing costs related with prescription of these drugs as they are frequently prescribed. Studies from the US, Australia and Europe have confirmed overuse of PPIs in hospitalized patients and in primary care[5,9]. The suitability or appropriateness of PPI prescription is as low as 19%. PPIs are being used indiscriminately in both the intensive and non-intensive care settings. This is due to poor implementation and low compliance with the guidelines[5].

One important factor for the widespread use of PPI is the administration of a PPI medication during a patient's hospitalization and its continuation in primary care without proper reason. The dramatic increase in PPI prescribing patterns over the past several years has raised key questions relating to their appropriate utilization. In addition, concerns have been raised related to the inappropriate use of the intravenous (IV) route of administration and to a lesser extent incorrect doses and length of therapy. Furthermore, often patients are inappropriately discharged on PPIs which could potentially increase the risk of pneumonia and CDAD and metabolic interactions with several other drugs. Many patients admitted to general medical wards are also routinely placed on these drugs when neither their admission nor the comorbid diagnoses support their use for either treatment or prophylaxis[34,40].

Multiple variables should be taken into consideration before prescribing a proton pump inhibitor. These include the dosages, period of therapy and how often patients receiving a proton pump inhibitor for gastro-esophageal reflux disease (GERD) were also being treated with other medications which are known to worsen or cause GERD[39].

The federal agency for healthcare research and quality reported that PPI should be used only in patients with severe PUD, ZES and in H. pylori cases. But generally PPIs are used inappropriately for all kinds of ulcer and prophylaxis of ulcer. The sudden withdrawal of PPI leads to rebound hypersecretion of acid by parietal cells which lead to further complications[5].

A study reported that PPIs can increase susceptibility to infections by decreasing stomach acid[13]. Normal stomach acidity helps to protect against certain bacterial and viral infections. This natural phenomenon is blocked by the use of PPIs[41]. It is suspected that acid suppression results in insufficient elimination of pathogenic organisms. Therefore, it has been suggested that patients at higher risk of pneumonia should be prescribed PPIs only at lower doses and only when necessary[5].

Inappropriate recommendation of PPIs is a matter of concern. PPIs have slight side effects and few noteworthy drug interactions, and they are generally harmless for long-term treatment. PPIs are a chief economic burden for the healthcare system in many countries. PPIs are frequently used in patients who do not meet the criteria for appropriate use or for indications where less powerful, cheaper agents would be effective for the treatment of symptoms. There is high prevalence of inappropriate use of PPIs[42,43].

PPIs should be prescribed in accordance with evidence-based guidelines in order to keep down unnecessary costs and prevent adverse drug reactions, which are a particular concern in the elderly. Inappropriate prescriptions are a particular concern among elderly patients, who normally have multiple comorbidities, take many drugs and are at higher risk of adverse drug reactions. Closer evaluation of the underlying clinical conditions and prescribing patterns are therefore essential for a rational, cost-effective approach[44]. As the use of PPIs continues to rise,

appropriate prescribing of PPIs is important to reduce adverse events in patients. Even in patients with appropriate indications for PPI use, this drug class has been related to several adverse events and risks to patient health[10].

The above evidences about the overuse of PPIs and the problems associated with overuse of PPIs insisted to perform a study on appropriate use of PPIs. Thus, the present study is an attempt to evaluate the appropriateness in the usage of PPIs in the study site and to signify the role of pharmacist in reducing the use of PPIs.

OBJECTIVES

- To study the appropriateness of prescription of proton pump inhibitors in study site
- To compare cost of prescription of proton pump inhibitors
- To observe the prescription pattern of proton pump inhibitors
- To assess the drug-drug interactions in the prescriptions
- To assess implementation of guidelines in prescription

PLAN OF STUDY

The study was planned to be carried out for a period of ten months from November 2015 to August 2016. The proposed study has been designed to be conducted in the following 4 phases.

Phase I

- Selection of study site and department
- Literature survey
- Preparation of Protocol
- Obtaining consent from the hospital authorities

Phase II

- Designing of structured data entry format
- Data collection
- Documentation of collected data using the data entry format

Phase III

- Analysis of prescription pattern of PPIs in the study site
- Evaluation of the appropriateness in prescription of PPIs
- Analysis of occurrence of drug interactions associated with PPIs in prescriptions
- Interpretation and evaluation of the data

Phase IV

- Preparation of the project report and submission to the study department

METHODOLOGY

STUDY SITE

The proposed study entitled **"study on appropriateness and cost comparison of prescription of proton pump inhibitors in a tertiary care hospital"** was conducted at a 750 bedded multi-specialty hospital at Coimbatore. The hospital is unique and well known for its services to people who come from various parts of the country. The institution excels in diverse specialties like General Medicine, General Surgery, Obstetrics, Gynecology, Pediatrics and Neonatology, Orthopedics, Psychiatry, Neurology, Radiology, Cardiology, Cardiothoracic surgery, Pulmonology and Critical Care, Gastroenterology, Urology, Nephrology, E.N.T, Ophthalmology, Oncology, Dental and Maxillofacial surgery, Anesthesiology, Laparoscopic surgery, Physical Medicine and Rehabilitation, Diabetology and Surgical Gastro Enterology. The hospital has well-staffed Pharmacy and a Drug Information Centre.

The hospital is well equipped with the modern diagnostic facilities like somatum sensation (CT scan), MRI scan, Ultrasound Sonography, Digital Subtraction Angiography, PET scan, ECG, Treadmill, Colour Doppler etc. The hospital also has twelve well equipped hi-tech operation theatres, Intensive Care Unit, Intensive Cardiac Care Unit, Intensive Pulmonary Care Unit, Neonatal Intensive Care Unit, Catheterization laboratory performing diagnostic cardiac catheterization, Balloon Valvuloplasty, Coronary stenting, Kidney transplantation unit with Haemodialysis machines, assisted Reproductive Technology Centre, 24 hour working microbiological and pathological services, round the clock casualty and pharmacy services.

DEPARTMENT SELECTED FOR STUDY

The department selected for the study is the department of General Medicine. The department of General Medicine was selected after the pilot study which revealed more scope for the study in the department as the prescriptions of PPIs here are more. The Department of Pharmacy Practice provides services to the department of General Medicine and also has a good co-operation which added up reasons for selecting this department for the proposed study.

STUDY DESIGN

Prospective observational study on appropriateness and cost comparison of prescription of PPIs

STUDY PERIOD

Ten months, From November 2015 to August 2016

CONSENT FROM THE HOSPITAL AUTHORITIES

Every project work carried out in the hospital by the Pharmacy Practice department students has to be approved by the Dean of the hospital and should be informed to all physicians and other healthcare professionals of the hospital. A protocol of the study which included the objectives, methodology etc., was submitted to the Dean of the hospital. The authorization from the Dean was procured through his letter **[SRH/EC.5-8/2016-17 dated 26 FEBRUARY 2016] Annexure 1.** The study was conducted with the expert guidance of senior and junior physicians of the study department. The author was allowed to utilize the hospital facilities to follow up the cases in the selected department. All the health care professionals were well informed about the study program through the Dean's official circular.

LITERATURE SURVEY

An extensive literature survey was done regarding the study on appropriateness and cost comparison of prescription of PPIs. The literatures pertaining to the study were collected from various sources such as:

- Alimentary Pharmacology and Therapeutics
- Annals of Pharmacotherapy
- Archives of Internal Medicine
- Canadian Family Physician
- Canadian Pharmacists Journal
- Digestive Diseases and Sciences
- European Journal of Internal Medicine
- Indian Journal of Pharmacology
- Indian Journal of Pharmacy Practice
- Indo American Journal of Pharmaceutical Research
- International Journal of Clinical Practice
- International Journal of Medical Research and Health Sciences
- Journal of scientific and Innovative Research
- Quarterly Journal of Medicine
- Therapeutic Advances in Gastroenterology
- World Journal of Gastroenterology
- World Journal of Pharmaceutical Research

The IOWA Drug Information System (IDIS) which is available with Department of Pharmacy Practice was used to collect and collate the literatures pertaining to the study. Databases such as Micromedex, Science Direct, NIH Medscape, PubMed and NCBI were also widely used. Some textbooks used were:

- Clinical Pharmacy and Therapeutics by Roger Walker and Cate Whittlesea, 5th Edition, 2012
- Pharmacotherapy – A Pathophysiologic Approach by Joseph T Dipiro, 7th Edition, 2008
- Harrison's Principles of Internal Medicine, 16th Edition, 2005
- Essentials of Medical Pharmacology by K D Tripathi, 6th Edition, 2010

PATIENT SELECTION

Inclusion criteria

- Patients above 18 years old
- Patients prescribed with oral or intravenous PPI
- Patients willing to participate in the study

Exclusion criteria

- Patients not willing to participate in the study
- Patients with insufficient data in their records

PATIENT INFORMATION FORM

A patient information form was prepared to inform the patient or the care givers about the purpose and necessity of the study. The patients were assured that the confidentiality will be strictly maintained. The model of the information form is given in **Annexure 2** for reference.

PATIENT CONSENT FORM

A patient consent form was prepared and written consent was obtained from the patient or the care givers. The model of the consent form is given in **Annexure 3** for reference.

DATA ENTRY FORMAT

A specially designed data entry format was prepared and used to record the patient details, laboratory investigations and diagnosis. The data entry format included drug chart, cost comparison table, a table for assessment of appropriateness and drug interaction chart. The same is given in **Annexure 4** for reference.

METHOD

Regular ward rounds were carried out in all the wards of the General Medicine department. Each patient's medication profile was reviewed. Patients who qualified the inclusion criteria were briefed on the study with the help of the patient information form and if anyone was willing to participate in the study, the consent was obtained. The data from the medical chart were recorded in customized data entry form. The data was analysed to evaluate the appropriateness and to compare the cost of prescription. The FDA approved guidelines was used to assess the appropriateness in prescription of PPIs.

REPORT SUBMISSION

The report of the study after analysis of data was prepared and submitted to the study department for necessary modification in future therapy for safe and effective treatment.

RESULTS AND DISCUSSION

The proposed work entitled **"Study on appropriateness and cost comparison of prescription of proton pump inhibitors in a tertiary care hospital"** was a prospective observational study carried out in a 750 bedded multispecialty private corporate hospital. A total of 209 patients who met the inclusion criteria were included in the study.

GENDER CATEGORIZATION

The gender categorization of the study population reveals 117 (55.98%) were males and 92 (44.02%) were females **[Table 2]**. The study result reveals that there is not much difference in prescription pattern of PPIs between males and females. A similar study conducted by **Afif et al (2007)[45]** reported 61% of the study population were males and 39 % were females.

AGE CATEGORIZATION

The age categorization was analysed. Majority of patients, i.e., 84 (40.19%) were in the age group >60 years, followed by 76 (36.36%) in the age group 41 – 60 years, 38 (18.19%) in the age group 21 – 40 years and the least number of patients 11 (5.26%) were in the age group below 20 years **[Table 3]**. The result reveals more number of PPIs were prescribed to patients above 40 years. A similar study was conducted by **Blesson M et al (2015)[20]** which reported that 42.16% comprised of patients in the age group of 60-80 years and 38.12% patients were in the age group of 40-60 years.

RISK FACTORS ASSOCIATED WITH USE OF PPIs

The patients were categorised based on the risk factors associated with use of PPIs. The results show that 78 patients (37.32%) were smokers, 48 patients (22.96%) were elderly, 43 patients (20.57%) were having stress related profession, 30 patients (14.35%) were chronic NSAID users and 29 patients (13.88%) were alcoholics **[Table 4]**.

The study population was categorised under different risk groups based on the number of risks. The different risks in the study population was found to be age, stress related profession, use of alcohol, smoking and chronic NSAID users. The patients were categorised into 4 main groups, i.e. no risk, moderate risk, high risk and very high risk categories. Majority of the patients 83 (39.71%) came under the moderate risk category, followed by 64 patients (30.62%) in the low risk category, 52 patients (24.88%) in the high risk category and 10 patients (4.79%) in the very high risk categories **[Table 5]**.

COMORBID DISEASE CONDITIONS

The comorbidities of the study population were analysed. The major comorbid condition found is DM [60 patients (28.71%)], followed by SHT in 51 (24.40%), Cardiac disorders in 24 (11.48%), Renal failure in 21 (10.05%), Respiratory infections in 18 (8.61%), Viral fever in 13 (6.22%) and others **[Table 6]**. Among the comorbid conditions observed DM, SHT, UTI, TB and anaemia are found to be major associated diseases where multiple drug therapy is involved which necessitates prophylactic use of PPI.

DURATION OF HOSPITAL STAY

The study population was analysed for the number of days of stay at the hospital and majority of patients 89 (42.57%) were admitted at the hospital for 3-5 days, followed by 66 patients (31.57%) were admitted for 5-7 days, 35 patients

(16.77%) were admitted for more than 7 days and 19 patients (9.09%) were admitted for lesser than 3 days **[Table 7]**. The number of increment in hospital stay indirectly involves with high cost associated with PPI use, because if IV line are available the PPIs are prescribed as parenteral which is higher compared to tablets.

DRUGS PRESCRIBED

The total number of drugs prescribed for the study population was found to be 2024. A total of 285 (14.08%) antibiotics were prescribed, followed by 209 (10.33%) PPIs, 155 (7.65%) anti-diabetics, 132 (6.32%) anti-hypertensives, 129 (6.18%) NSAIDs, 115 (5.51%) anti-emetics, 97 (4.65%) vitamin supplements, 81 (3.88%) intravenous fluids, 79 (3.78%) anti-platelets and anti-coagulants, 75 (3.59%) hypolipidemics and other agents **[Table 8]**. From the results it is observed that antibiotics are the most concomitantly prescribed with PPIs in the study population. **Krishna K J et al (2016)[19]** similarly reported more percentage of antibiotics (28.25%) used concomitantly with PPIs. It is observed that as the number of drugs prescribed increases there is more chance for prescribing PPI for prophylactic prevention of PUD or gastric irritation.

CATEGORIZATION OF PPIs PRESCRIBED

Among the 209 PPIs prescribed in the study population pantoprazole was the most frequently prescribed 144 (68.89%). Esomeprazole 46 (22.01%) comes next in line followed by rabeprazole 17 (8.13%) and omeprazole 2 (0.95%) **[Table 9]**. The result reveals that pantoprazole is the most frequently prescribed PPI in the study site and omeprazole is the least prescribed PPI. A similar study was conducted by **Anton P et al (2016)[18]** in which 82% patients were prescribed pantoprazole. A study by **Jungnickel P W (2000)[46]** stated that pantoprazole has

low potential for drug interactions compared to other PPIs. Thus prescribing pantoprazole more is found to be beneficial, which avoids risk of drug interactions.

DOSAGE FORMS OF PPIs PRESCRIBED

PPIs are available in the form of tablets and injections. In the study population both the tablets as well as parenteral PPIs were prescribed. Majority of patients, i.e., 92 (44.02%) were prescribed a combination of both parenteral and tablet dosage forms of PPIs. There were 68 (32.54%) patients prescribed tablets alone and 49 (23.44%) patients were prescribed parenteral alone **[Table 10]**. The similar result was observed in a study carried out by **Shobha C et al (2014)**[24] which reported that parenteral use of PPI was less. The use of tablet dosage form is recommended in studies which report that tablets are cost effective than parenteral preparations. The assessment of effectiveness and obstacles of taking tablet by the patient can be done before prescribing PPIs which in turn will reduce the cost of therapy.

DOSING FREQUENCY OF PPIs PRESCRIBED

Assessment of dosing frequency of PPIs prescribed revealed that in 95 prescriptions twice daily dosing of pantoprazole was prescribed and in 49 prescriptions once daily dosing of pantoprazole was prescribed. In the case of esomeprazole twice daily dosing was prescribed in 30 prescriptions, once daily dosing of esomeprazole was prescribed in 15 prescriptions and one patient was prescribed three times a day dose of esomeprazole. Once daily dosing of rabeprazole was prescribed in 8 prescriptions and twice daily rabeprazole was prescribed in 9 prescriptions. Omeprazole was prescribed as twice daily in 2 prescriptions **[Table 11]**. As per FDA guidelines **[Table 1]** twice daily dosing of

pantoprazole is inappropriate, once daily dosing is sufficient to produce desired effects. Thus, twice daily dosing of pantoprazole in the study department was changed to once daily dosing by making necessary intervention with physician.

EVALUATION OF APPROPRIATENESS IN USE OF PPIs

Appropriateness of prescription of PPIs in the study population was analysed using the FDA guidelines **[Table 1]**, out of 209 patients 115 (55.02%) were found to be appropriately prescribed with PPIs, which indicates there is recommended conditions as mentioned in guidelines and 94 (44.98%) prescriptions were found to be inappropriate, i.e., there was no necessary indication of PPI use as per the guidelines **[Table 12]**. Similar results were found out by **Blesson M et al (2015)[20],** which reported that 60.41% patients had appropriate prescription of PPI and 39.58% patients had inappropriate prescription of PPIs.

Among the prescription with appropriate use of PPIs the indications were analysed and it revealed that PPIs were utilised for the prophylactic indication in 53 (46.08%) patients where polypharmacy was there in their prescription, followed by 44 (38.26%) prescription had NSAIDs and 9 cases (7.83%) diagnosed with AGE. The PPIs were prescribed very less in case of PUD. The result reveals that 4 patients (3.48%) diagnosed with gastritis were prescribed with PPI followed by 3 patients (2.61%) with duodenal ulcer and 2 patients (1.74%) suffering from APD were prescribed with PPIs **[Table 13]**. Thus the results reveal that more number of patients was prescribed with PPIs for the prevention of ulcer rather than treating ulcer. This result was supported by a study carried out by **Nousheen et al (2014)[23]** in which 58% patients received PPIs for the prophylactic indications. Thus the prophylactic use of PPIs can be evaluated and if alternatives are available that can be utilised in order to lower the risk involved with PPI use.

The inappropriate prescriptions with PPIs were analysed and it was found that inappropriateness in prescriptions may be due to several reasons, i.e. wrong frequency, wrong dosage form, availability of alternative, prolonged duration of treatment, inappropriate indication and occurrence of adverse events. Majority of the inappropriate prescriptions involved pantoprazole followed by esomeprazole and rabeprazole **[Table 14]**. The inappropriateness identified were documented and the management measures were taken to prevent inappropriate prescription through proper intervention

COST COMPARISON

A wide variety of PPIs are available in the study site and the cost of each PPI also varies. Analysis of the cost of different parenteral PPIs, oral PPIs and H_2RAs available was carried out. The result of cost comparison showed that among IV PPIs injection Esomac (Esomeprazole) was the most costly (Rs. 92.5) and injection Pantocid (Pantoprazole) was the least costly (Rs. 43.38) drug. Among oral PPIs tablet Pantocid L (Pantoprazole) was the most costly (Rs. 18.12) and tablet Omez (Omeprazole) was the least costly (Rs. 3.49). The cost of H_2RAs were also analysed and it is found that the H_2RAs are cheaper than PPIs. Wherever possible the use of H_2RAs is recommended instead of the more costly PPIs. The cost of treatment can be reduced in 94 patients who have been prescribed with PPIs inappropriately **[Table 15]**. Among these 94 patients, 71 patients were identified with H_2RAs as an alternate drug instead of PPI by which the cost of treatment will be reduced. An unnecessary healthcare cost to the patient is a matter of concern and necessary action must be taken. The possibility of alternate and reducing the cost of treatment was reported to the study department and immediate interventions were implicated.

DRUG INTERACTIONS

Drug interactions associated with PPIs were analysed. A total of 157 drug interactions were identified which consisted of 3 major interactions, 153 moderate interactions and 1 minor interaction **[Table 16]**. Out of 157, 21 different types of interactions associated with PPIs were identified of which the most common interaction was that of clopidogrel and pantoprazole, followed by atorvastatin and pantoprazole and others.

From the results it can be observed that a high degree of appropriateness is seen in use of PPIs in the study department. The possible reason of inappropriateness were identified and reported to the study department. The results signified the importance of the role of the clinical pharmacist in monitoring the prescriptions with PPIs. The study also warrants the need for developing guidelines for PPI use. Even though there are no major risks seen in study population by the use of PPI but rational prescribing of PPI will reduce overall cost of therapy as well as improves the patient safety.

Table 2: Distribution of Patients Based on Gender (N=209)

Sl. No.	Gender	Number (N)	Percentage (%)
1.	Male	117	55.98
2.	Female	92	44.02

Figure 1: Gender (N=209)

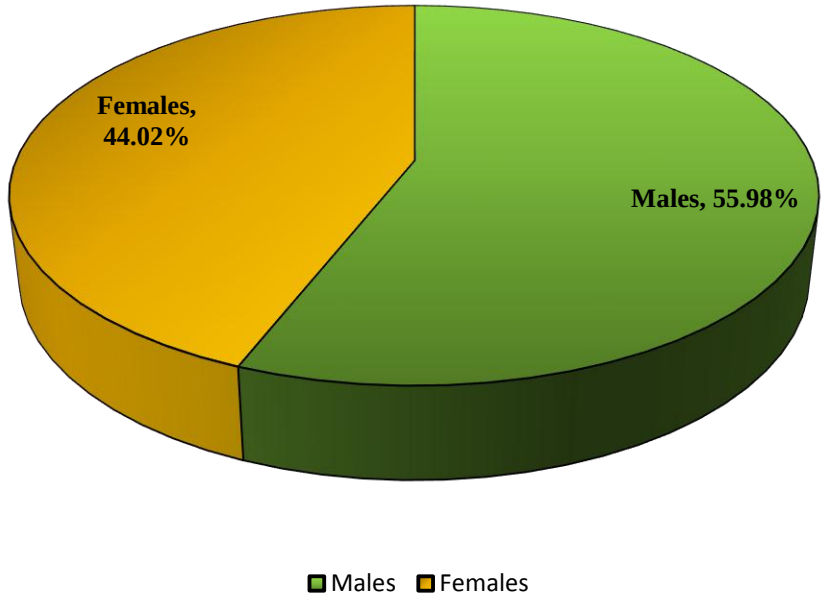

Table 3: Distribution of Patients Based on Age (N=209)

Sl. No.	Age	Number (N)	Percentage (%)
1.	Less than 20 years	11	5.26
2.	21 – 40 years	38	18.19
3.	41 – 60 years	76	36.36
4.	More than 60 years	84	40.19

Figure 2: Age (N=209)

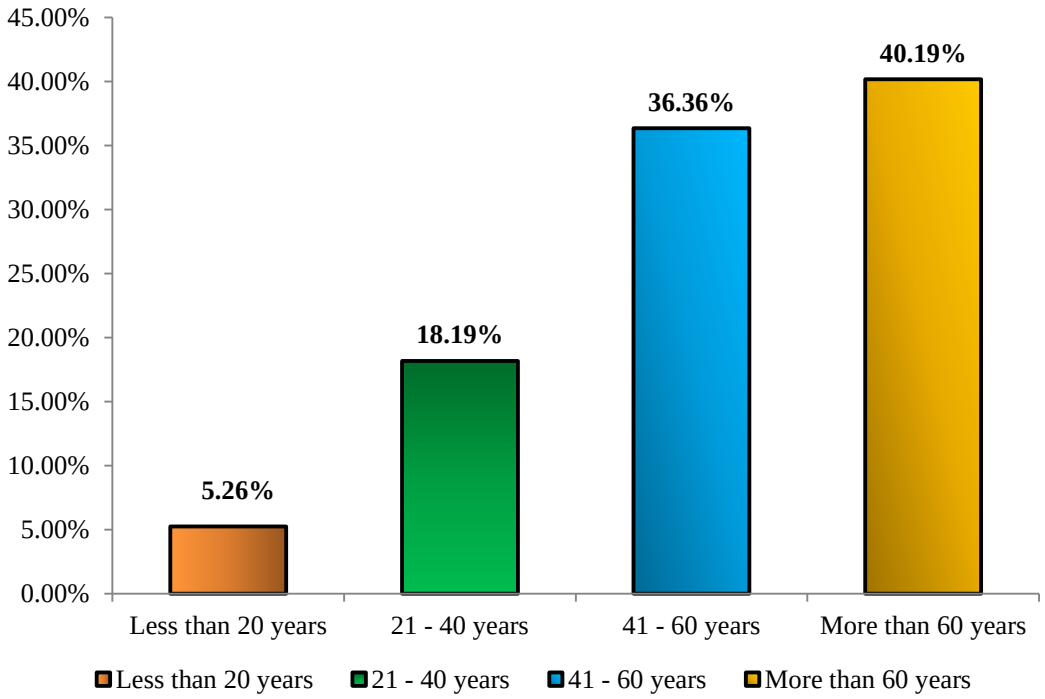

Table 4: Risk Factors associated with use of PPIs (N=209)

Sl. No.	Risk Factors	Number (N)	Percentage (%)
1.	Age	48	22.96
2.	Alcoholic	29	13.88
3.	Smoker	78	37.32
4.	Stress	43	20.57
5.	Chronic use of NSAIDs	30	14.35

Figure 3: Risk Factors associated with use of PPIS

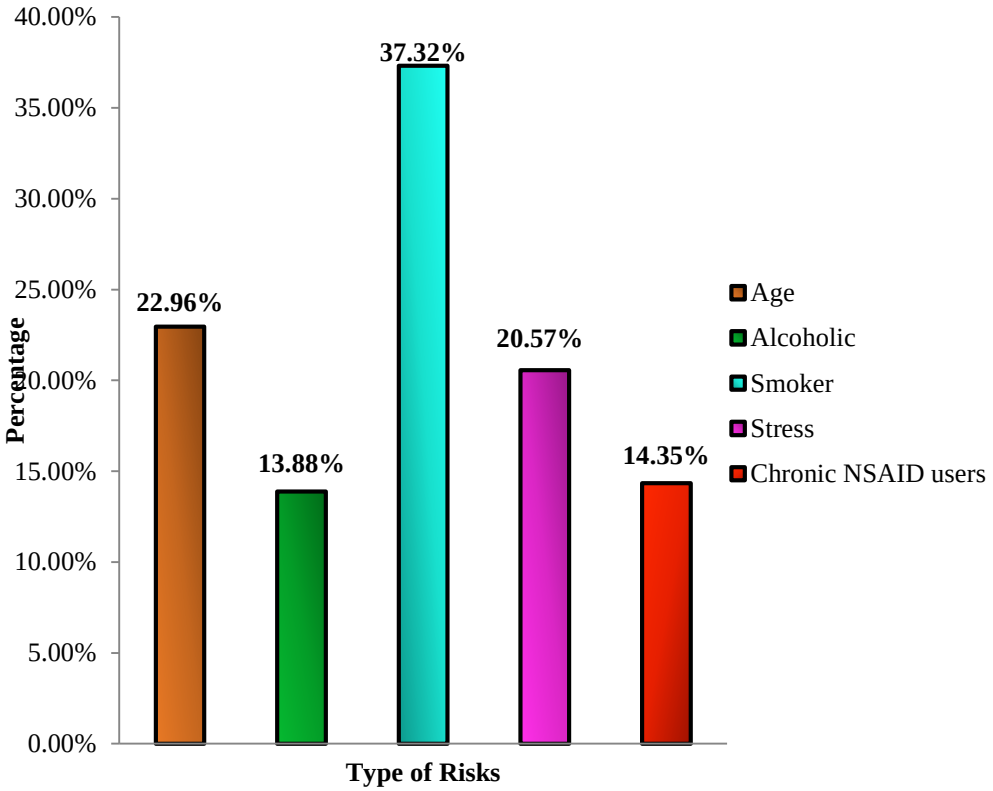

Table 5: Risk Categorization (N=209)

Sl. No.	Risk Categories	Number (N)	Percentage (%)
1.	No Risk (no risk factors)	64	30.62
2.	Moderate Risk (1 risk factor)	83	39.71
3.	High Risk (2 risk factors)	52	24.88
4.	Very High Risk (more than 2 risk factors)	10	4.79

Figure 4: Risk Categorization

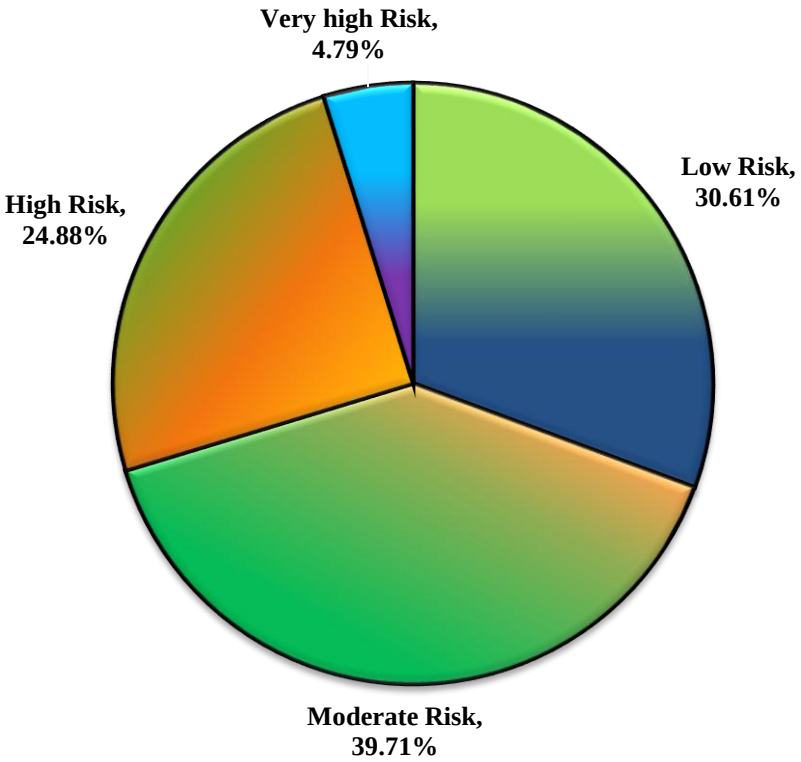

Table 6: Comorbid Disease Conditions (N=209)

Sl. No.	Comorbid Conditions	Number (N)	Percentage (%)
1.	DM	60	28.71
2.	SHT	51	24.40
3.	Cardiac Disorders	24	11.48
4.	Renal Failure	21	10.05
5.	Respiratory Infections	18	8.61
6.	Viral Fever	13	6.22
7.	Stroke	13	6.22
8.	Anaemia	12	5.74
9.	Seizure	10	4.78
10.	UTI	10	4.78
11.	CVA	8	3.83
12.	TB	5	2.39
13.	COPD	4	1.91
14.	Diabetic Ketoacidosis	3	1.44
15.	Malaria	3	1.44
16.	Hypothyroidism	3	1.44
17.	Cirrhosis	2	0.96
18.	Jaundice	2	0.96

Table 7: Duration of Hospital Stay (N=209)

Sl. No.	Duration of Stay	Number (N)	Percentage (%)
1.	Lesser than 3 days	19	9.09
2.	3 – 5 days	89	42.57
3.	5 – 7 days	66	31.57
4.	More than 7 days	35	16.77

Figure 5: Duration of Hospital Stay

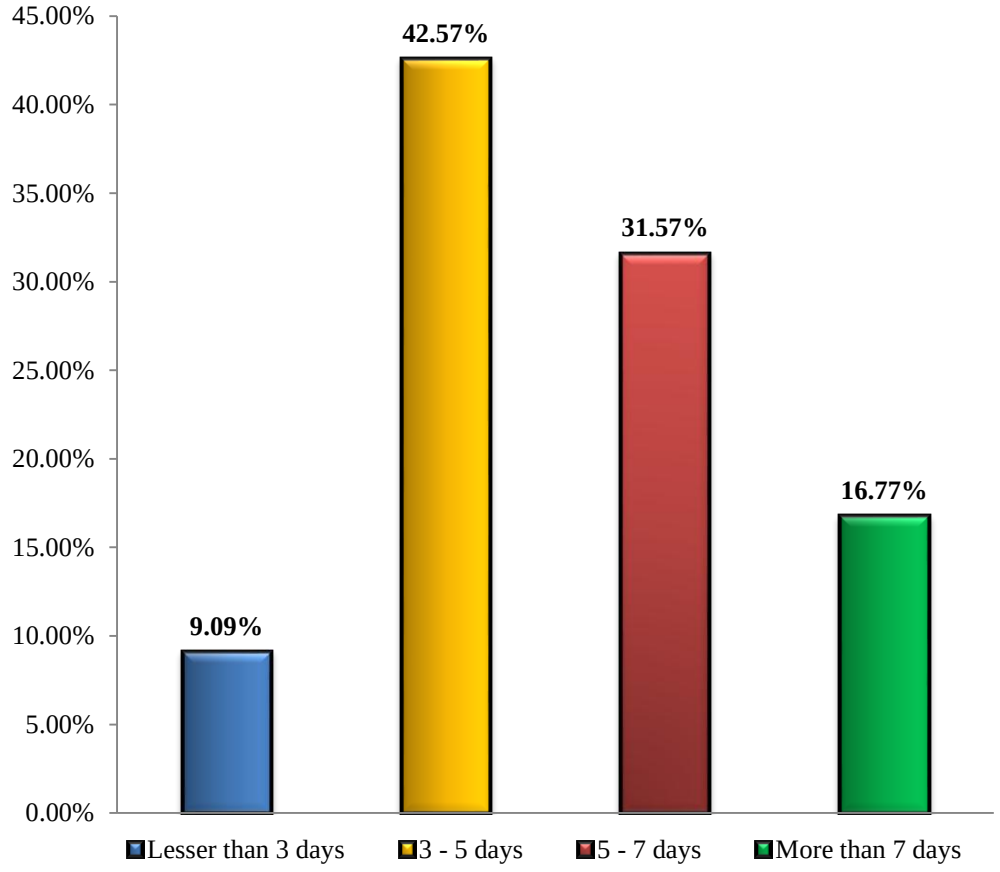

Table 8: Drugs prescribed (N=2024)

Sl. No.	Drug Class	Number (N)	Percentage (%)
1.	Antibiotics	285	14.08
2.	PPIs	209	10.33
3.	Anti-diabetics	155	7.65
4.	Anti-hypertensives	132	6.32
5.	NSAIDs	129	6.18
6.	Anti-emetics	115	5.51
7.	Vitamin supplements	97	4.65
8.	Intravenous fluids	81	3.88
9.	Antiplatelets and Anticoagulants	79	3.78
10.	Hypolipidemics	75	3.59
11.	Probiotics	74	3.55
12.	Calcium supplements	69	3.31
13.	Antiepileptics	58	2.77
14.	Bronchodilators	45	2.16
15.	Sedatives	44	2.11
16.	Diuretics	41	1.96
17.	Antacids	31	1.48
18.	Laxatives	25	1.19
19.	Cardiovascular agents	25	1.19
20.	Protein supplements	24	1.15
21.	Corticosteroids	22	1.05
22.	Antidiarrhoeals	17	0.81
23.	Opioids	14	0.67
24.	Anti-gout agents	13	0.62
25.	Liver protectives	12	0.57
26.	Anti-tussives	11	0.53
27.	Anti TB agents	10	0.47
28.	Iron supplements	8	0.38
29.	Antimalarials	6	0.28
30.	Others	118	5.65

Table 9: PPIs Prescribed (N=209)

Sl. No.	PPIs	Number (N)	Percentage (%)
1.	Pantoprazole	144	68.89
2.	Esomeprazole	46	22.01
3.	Rabeprazole	17	8.13
4.	Omeprazole	2	0.95

Figure 6: PPIs Prescribed (N=272)

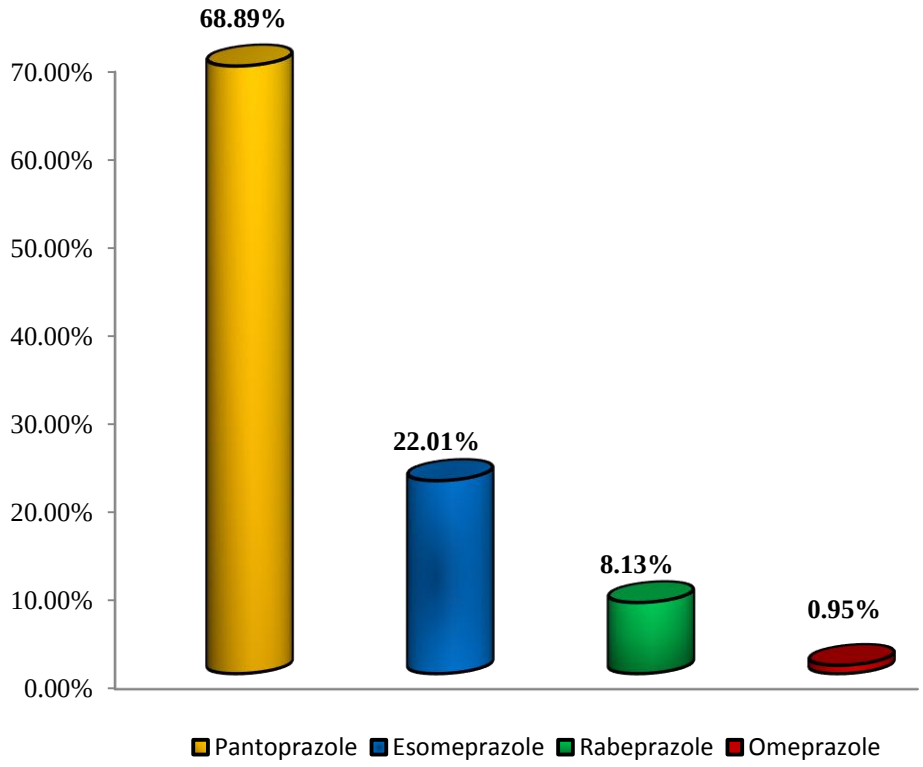

Table 10: Distribution of Dosage forms of PPIs prescribed (N=209)

Sl. No.	Dosage Form	Number (N)	Percentage (%)
1.	IV	49	23.44
2.	Oral	68	32.54
3.	Combination	92	44.02

Figure 7: Dosage Forms

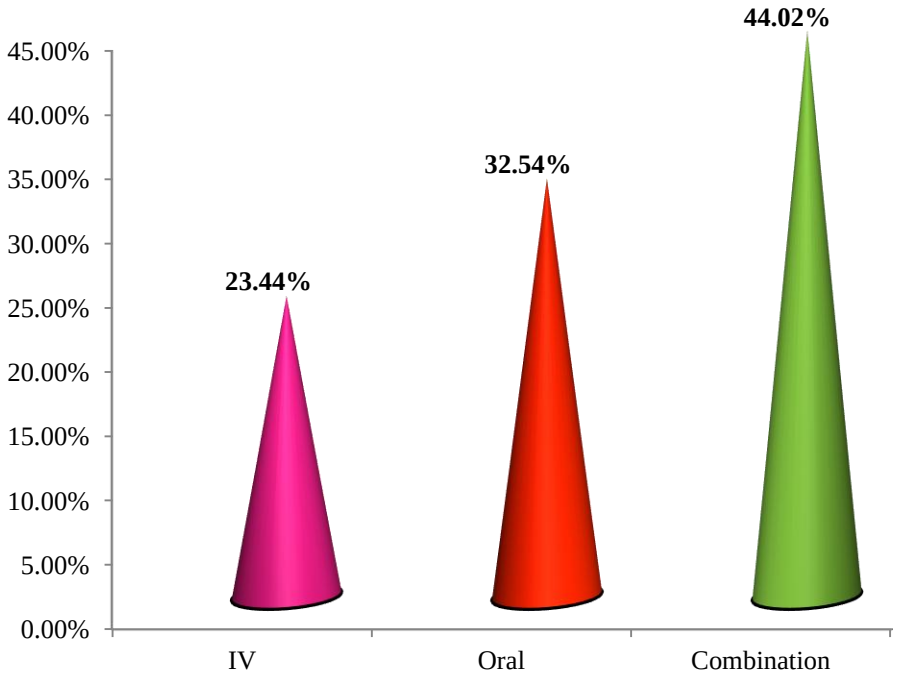

Table 11: Dosing Frequency of PPIs Prescribed (N=209)

Sl. No.	PPIs Prescribed	Frequency		
		O.D	B.D	T.I.D
1.	Pantoprazole	49	95	-
2.	Esomeprazole	15	30	1
3.	Rabeprazole	8	9	-
4.	Omeprazole	-	2	-

Figure 8: Dosing Frequency of PPIs Prescribed

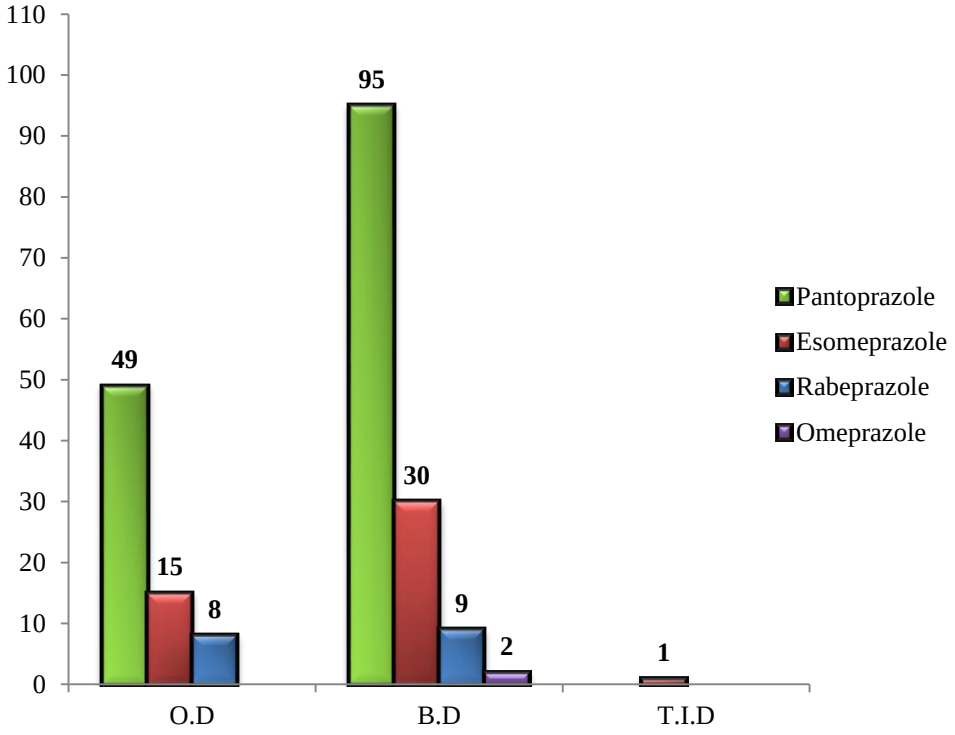

Table 12: Evaluation of Appropriateness (N=209)

Sl. No.	Appropriateness	Number (N)	Percentage (%)
1.	Appropriate	115	55.02
2.	Inappropriate	94	44.98

Figure 9: Evaluation of Appropriateness

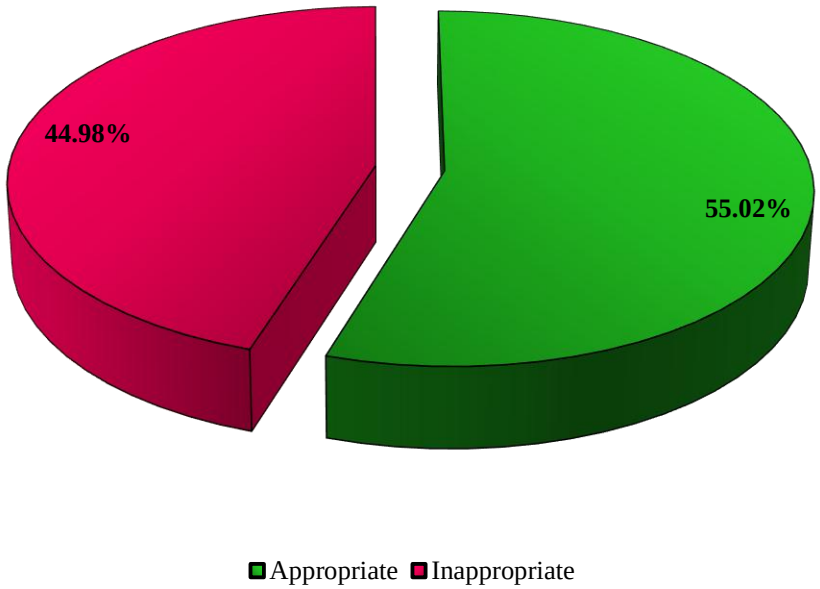

Table 13: Categorization of Appropriate Indications of PPI use (N=115)

Sl. No.	Indications	Number (N)	Percentage (%)
Ulcer Related Events			
1.	Gastritis	4	3.48
2.	Duodenal Ulcer	3	2.61
3.	APD	2	1.74
Prophylactic Indications for the use of PPIs			
4.	NSAIDs	44	38.26
5.	Polypharmacy	53	46.08
6.	AGE	9	7.83

Table 14: Categorization of Inappropriate Use of PPIs

Sl. No.	PPIs involved in Inappropriate Prescribing	Inappropriateness Identified	Number (N)
1.	Pantoprazole	1. Wrong Frequency	23
		2. Wrong Dosage Form	10
		3. Availability of Alternative	42
		4. Prolonged Duration of Treatment	31
		5. Inappropriate Indication	22
		6. Occurrence of Adverse Event	14
2.	Esomeprazole	1. Wrong Dosage Form	4
		2. Availability of Alternative	16
		3. Inappropriate Indication	8
		4. Prolonged Duration of Treatment	11
		5. Occurrence of Adverse Event	11
3.	Rabeprazole	1. Availability of Alternative	13
		2. Inappropriate Indication	11
		3. Occurrence of Adverse Event	9

Table 15: Cost Comparison of PPIs Prescribed

S.No.	Prescribed PPI	Cost/Unit (in Rs.)	Recommended alternative	Cost/Unit (in Rs.)	No. of patients
1	Inj. Esomac	92.5	Inj. Aciloc	3.29	16
2	Inj. Pantocid	43.38	T. Zinetac	1.34	14
3	Inj. Pan	56.61	Inj. Rantac	13.35	13
4	Inj. Happi	65	Inj. Aciloc	3.29	13
5	T. Pantocid	7.9	T. Histac	1.22	9
6	Inj. Pan	56.61	T. Pan	7.7	8
7	Inj. Esomac	92.5	Inj. Raciper	49	7
8	T. Pantodac	9.55	T. Rantac	0.72	6
9	Inj. Raciper	49	T. Neksium	9.90	4
10	Inj. Pantocid	43.38	T. Pantodac	9.55	4

Table 16: Drug Interactions (N=157)

S.No.	Interacting Drugs	Interaction	Severity	Number
1	Clopidogrel + Esomeprazole	May reduce cardio-protective effect of clopidogrel	Major	3
2	Clopidogrel + Pantoprazole	May reduce cardio-protective effect of clopidogrel	Moderate	34
3	Atorvastatin + Pantoprazole	May increase plasma concentration of atorvastatin and increase risk of myopathy	Moderate	31
4	Aspirin + Pantoprazole	May decrease oral bioavailability of aspirin	Moderate	26
5	Torsemide + Pantoprazole	May increase risk of hypomagnesemia	Moderate	10
6	Furosemide + Pantoprazole	May increase risk of hypomagnesemia	Moderate	8
7	Amikacin + Esomeprazole	May increase risk of hypomagnesemia	Moderate	8
8	Cefpodoxime + Esomeprazole	Oral bioavailability of cefpodoxime may be reduced	Moderate	7
9	Digoxin + Pantoprazole	May increase blood levels of digoxin and increase its effects	Moderate	6
10	Amikacin + Pantoprazole	May increase risk of hypomagnesemia	Moderate	5
11	Oxcarbazepine + Pantoprazole	May increase plasma concentration of pantoprazole	Moderate	5
12	Cefpodoxime + Pantoprazole	Oral bioavailability of cefpodoxime may be reduced	Moderate	2

S.No.	Interacting Drugs	Interaction	Severity	Number
13	Ferrous fumarate + Pantoprazole	Absorption of iron may be impaired	Moderate	2
14	Iron + Esomeprazole	Absorption of iron may be impaired	Moderate	2
15	Rifampicin + Esomeprazole	May decrease plasma concentration of esomeprazole	Moderate	2
16	Phenytoin + Esomeprazole	May increase plasma concentration of phenytoin	Moderate	1
17	Theophylline + Esomeprazole	Rate of absorption of theophylline may be increased	Moderate	1
18	Theophylline + Pantoprazole	Rate of absorption of theophylline may be increased	Moderate	1
19	Torsemide + Rabeprazole	May increase risk of hypomagnesemia	Moderate	1
20	Warfarin + Pantoprazole	May increase INR and prothrombin time	Moderate	1
21	Aspirin + Rabeprazole	Oral bioavailability of aspirin may be decreased	Minor	1

CONCLUSION

The study on appropriateness and cost comparison of prescription of PPIs was successfully carried out. Most of the PPI prescriptions are found to be appropriate at the study site. The interventions made by the pharmacist avoided the inappropriate use of PPI at the study site. Most of the inappropriate prescriptions were consisting increased frequency of dosing and utilising PPIs for prophylactic use. Reducing PPI use will prevent the risk associated with PPIs and also reduce cost involved with its use.

To conclude, the present study suggests that physician and clinical pharmacist should work together to increase appropriate use of PPIs. The inappropriate use of PPIs must be prevented through proper interventions. The development of guidelines for PPI usage will avoid irrational prescription of PPIs and reduce cost of therapy. The need for PPI use in the individual patient must be evaluated by the pharmacist and if any possible alternatives are found to be effective the same can be reported to the physician.

The appropriate use of PPIs will ensure the patient safety by reducing the risks associated with unnecessary prescription of PPIs. The regular monitoring of prescription of PPI by clinical pharmacist is the need of the hour.

FUTURE OUTLOOK

The present study reveals some extent of inappropriate use of PPIs. There is no established Indian guideline regarding the use of PPIs. Hence in future it is necessary to prepare institutional guideline for the use of PPI and evaluation can be done based on the new implemented guideline in different setup. The impact and risk involved with overuse of PPI has not been thoroughly revealed, so studies which focus on the impact of chronic use of PPIs are necessary to determine the risk associated with long term usage of PPIs.

The comparative studies on PPIs and alternatives will be useful to reduce the use of PPIs and thereby reduce the risk as well as cost. The future pharmacoeconomical analysis of PPIs will be useful to decide the PPI use in patient with poor economy.

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